Please amend claim 39 as follows:

39. (once amended) [A]The method of claim 38 wherein the non-polymeric particulate matrix is selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, and ceramic particles.

Remarks

Claims 2–6 and 38–40 are pending in the captioned application. Claims 8–37 have been withdrawn from consideration. A Request for Continuing Examination has been filed and it is respectfully requested that it be granted. Applicants have amended claims 4, 6, 38 and 39. Applicants respectfully reassert that the amendments are fairly based on the specification, and respectfully request their entry.

The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner states, "in claim 38, the recitation of 'a method of embolus therapy comprising a composition' is confusing because it appears to be grammatically incorrect. It appears to be missing an administration step."

In response, Applicants have amended claim 38 to recite "introducing a composition." Applicants respectfully submit that this amendment overcomes the Examiner's rejection.

The Examiner has objected to claim 4 stating it recites, "the limitation 'said reduced perfusion' in line 3," maintaining "there is insufficient antecedent basis for this limitation in the claim."

In response, Applicants have amended claim 4 to recite "said composition" in place of "said reduced perfusion." Applicants respectfully assert that this overcomes the Examiner's rejection.

The Examiner has objected to claim 5 stating, "the recitation that the particles 'comprise an insoluble phosphate salt' is confusing because it is not clear if the particles further comprise such a salt or if this phosphate salt is further defining the non-polymeric particulate matrix as set forth in the base claim (claim 38)."

In response, Applicants fail to understand what the Examiner is objecting to here. Specifically, the claim states that the "said water-insoluble particles" comprise the "insoluble phosphate salt." The claim refers back to claim 38, which specifically contains the recitation "water insoluble particles." Thus, Applicants respectfully submit that one skilled in the art would recognize that the "water insoluble particles," as recited in claim 5, would include an insoluble phosphate salt having the recited formula.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claim 6 stating that "the limitation 'said insoluble phosphate salt,' " does not have sufficient "antecedent basis for this limitation in the claim."

In response, Applicants have amended the dependency of claim 6 to be dependent upon claim 5, which contains this recitation. Applicants respectfully assert that this overcomes the Examiner's rejection, which should be withdrawn.

The Examiner has rejected claims 2–6 and 38–40 under 35 U.S.C. § 102(b) as "being anticipated by Sumiaki (Japanese Patent 63255231), for the reasons set forth in the office action mailed 1/8/2001." In that Action, the Examiner stated, "Sumiaki discloses a method of embolus therapy comprising administering a composition comprising particles of hydroxyapatite having a size of 10 to 1000 um, see pages 3-4. The method further includes diagnostic imaging to detect the location of the embolus, wherein the particles have contrast media function ..."

In response to this, the Applicants asserted that the embolus agents disclosed in the reference are intended to be therapeutic agents which include a therapeutic antineoplastic agent (see e.g., page 5). Applicants pointed out that such is not the nature

of the instant invention, which is a method for introducing contrast agents to a particular site of interest using embolus-generating agents. Applicants conceded that the Sumiaki reference does disclose the use of diagnostic imaging to detect the location of the embolus, but pointed out that there was no disclosure, nor even any suggestion, that the embolytic particles should contain a diagnostically effective compound for use in the imaging procedure. Indeed, no such agent is included in the Sumiaki reference disclosure since the reference specified that the embolytic particles are to include the therapeutic (antineoplastic) compositions to be delivered to a desired site.

In response, the Examiner states, "this is not found persuasive because it is noted that the instant claims use the term 'comprising' to describe the embolism composition, which would not exclude the anti-neoplastic agent which is absorbed on the surface of the particles. While the claims use the terminology 'consisting essentially of' in describing the particles, this use would not exclude the anti-neoplastic agent, which is absorbed onto the particles disclosed by Sumiaki for several reasons. First the anti-neoplastic agent is not part of the microparticles, but is absorbed onto the particles. Second, the phrase 'consisting essentially of ' only excludes ingredients that would affect the basic and novel characteristics of the product as defined in the claim...this is not the case in the instant situation, since the inclusion of the anti-neoplastic agent would not effect the embolizing characteristic of the particles disclosed by Sumiaki. Also, the phrase 'consisting essentially of ' does not mean 'consisting solely of.'...The phrase 'consisting essentially of ' does not limit the claims so as to exclude other things when the specification clearly indicates other constituents may be present."

The Examiner continues, "applicant further asserts that the embolytic particles disclosed by Sumiaki do not include a diagnostically effective compound, rather the particles themselves are diagnostically effective. This is not found persuasive because, 'a non radioactive diagnostically effective compound,' given its broadest reasonable interpretation, would mean any compound which is effective for providing diagnosis. Thus, since the particles disclosed by Sumiaki are diagnostically detectable, they inherently contain a (non-radioactive) diagnostically effective compound. For example, since the particles then selves are diagnostically detected, the particles must contain a compound which diagnostically effective."

In response, Applicants respectfully assert that the Examiner is reading something into the Sumiaki reference that is not there. Specifically, claim 38 and all claims dependent thereon, specifically state that the particles consist essentially of "a non-radioactive diagnostically effective compound or solution thereof encapsulated in a non-polymeric particulate matrix." Such is neither disclosed nor even suggested by Sumiaki, which merely discloses a therapeutic agent in combination with the embolus-generating particulates. Applicants continue to concede that the Sumiaki reference does disclose the use of imaging to detect the location of the embolus; however, such is quite different from the diagnostically effective compound which is used for diagnostic imaging as defined in the instant invention. Indeed, there is neither disclosure, nor even any suggestion of any diagnostic utility for the Sumiaki particles.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claims 2–6 and 38–40 under 35 U.S.C. § 102(b) as "being anticipated by Tsuru (US Pat. 5,055,307), for the reasons set forth in the office action mailed 1/8/2001."

In that Office Action, the Examiner stated, "Tsuru discloses a method of embolus therapy comprising administering a composition comprising particles of hydroxyapatite having the size of 5 to 1000 um, and performing diagnostic imaging to detect the location of the embolus … ."

In response, Applicants respectfully noted that, like the Sumiaki reference, the disclosure of the Tsuru reference is also directed to delivery of drugs (**therapeutic** agents) at the site of the embolus, and not the use of the embolytic particles containing a contrast agent for imaging purposes. While Applicants conceded that the reference suggests that the particles might be useful for imaging purposes, there was no disclosure or even any suggestion in the reference that the particles could be utilized for diagnostic imaging nor contain a diagnostic imaging agent as in the instant invention. Indeed, Applicants pointed out at column 5, the patent specifically states "the drug delivery granules have no toxicity to a human body having excellent imaging property to an x-rays or ultrasonic waves, and can easily be traced after the application thereof (column 5, lines 30-35)", indicating that the particles themselves, and not a contained imaging agent,

contribute to the imaging technique. Further, Applicants also noted that there was no contemplation in the reference for inclusion of any imaging agent.

The Examiner has stated, "this is not found persuasive because Tsuru clearly discloses that the particles are used in methods of embolus therapy..." The Examiner continues, "since the particles have excellent imaging properties for X-ray and ultrasound imaging, such particles inherently contain a 'diagnostically effective compound' as claimed. For example, the compounds used to make the particles disclosed by Tsuru are 'diagnostically effective' when in particulate form.

The Examiner continues, "applicants further assert that there is no contrast agent contained in the particles themselves but that the particles are administered in a suspension of contrast agent. This is not found persuasive because the particles themselves are capable of being diagnostically effective, thus contain a diagnostically effective compound. However, the use of the iodinated contrast agent disclosed in example 1 is within the scope of the instant claims. The particles disclosed by Tsuru are porous... Thus, the solution of iodinated contrast agent when added to the porous particles would fill the pores and be a solution encapsulated in the particulate matrix as instantly claimed."

In response, Applicants respectfully assert that the Examiner is reading more into the disclosure than is presented. Specifically, there is neither disclosure nor even any suggestion that the particles themselves can be used in conjunction with a "a non-

radioactive diagnostically effective compound or solution thereof encapsulated in a non-polymeric particulate matrix." More specifically, as stated previously, there is no disclosure of an inclusion of the diagnostic imaging agent in the particles. Further, in the Examiner's discussion of example 1, there is no reason to believe that the iodine would become "a solution encapsulated in the particulate matrix," because while the particles are disclosed as porous, there is no disclosure about the nature of the pores and what substances might, or might not, be admitted into the particulate matrix.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claims 2-6 and 38–40 under 35 U.S.C. § 102(b) as "being anticipated by Okada (EP 470569), for the reasons set forth in the office action mailed 1/8/2001." In that Action, the Examiner states, "Okada discloses a method of embolus therapy comprising administering a composition comprising particles having a size of 5 to 1000 um ... The particles comprise hydroxyapatite ... The particles may further comprise a contrast agent for imaging techniques ...."

In response, Applicants pointed out that the disclosure of the reference specifically stated (at page 8, lines 34 et seq.), "the intravascular embolizing agent of the present invention is used as it is, or by dispersing, before or at the time of use in a proper pharmaceutically acceptable character, for example, dispersing vehicle or a contrast medium such as lipodol." Thus, the cited reference does not disclose the particles contain

contrast agent, but rather (as was the case with the Tsuru reference), that the particles should be dispersed in a contrast agent, if desired for contrast purposes.

The Examiner has stated, "this is not found persuasive because when the porous particles disclosed by Okada are dispersed in a solution of contrast agent, the contrast agent would enter the pores and become encapsulated in a particulate matrix as claimed."

In response, Applicants respectfully assert that the Examiner, again, is reading something into the reference that is not disclosed. Specifically, while the particles are disclosed as porous, there is no discussion of the properties of the pores and what sort of materials would not would not "enter the pores and become encapsulated in a particulate matrix."

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 2–6 and 38–40 under 35 U.S.C. § 103(a) as "being unpatentable over any one of Sumiaki (JP 63255231), Tsuru (US Pat. 5,055,307) or Okada (EP 470569) in view of Meeh (WO 95.27437), for the reasons set forth in the office action mailed 1/8/2001."

In that Action, the Examiner stated, "Sumiaki, Tsuru and Okada disclose a method of embolus therapy comprising administering composition comprising particles

by hydroxyapatite having a size of 5 to 1000 um, and performing diagnostic imaging to detect the location of the embolus, as discussed above." The Examiner concedes, "Sumiaki, Tsuru and Okada fail to specifically disclose that the hydroxyapatite has the specific formula as instantly claimed." However, the Examiner continued, "Meeh discloses that hydroxyapatite compositions, having the formula shown on pages 4-5, are especially useful for various methods of imaging." The Examiner concluded, "it would have been obvious to one of ordinary skill in the art to use the hydroxyapatite compositions disclosed by Meeh as the hydroxyapatite compositions used in the methods disclosed by Sumiaki, Tsuru and Okada because Meeh teaches that such hydroxyapatite compositions...are especially useful for various methods of imaging."

In response, the Applicants reiterated the distinctions and remarks made with respect to each of the Sumiaki, Tsuru, and Okada references described under 35 U.S.C. § 102(b) objections above and submitted that the citation of the Meeh, et al. reference did nothing to remedy the deficiencies. Specifically, Applicants asserted that none of these references, alone or in combination with one another, disclosed, or even suggested, the method of the instant invention, which includes the utilization of embolytic particles containing a contrast agent.

In response, the Examiner has stated that Applicants arguments are not found persuasive because the "primary references do disclose a method that is encompassed by the claims for the reasons, as addressed above."

In response, Applicants reiterate the arguments presented above, and respectfully submit that the Examiner is reading more into the primary references than they disclose. Specifically, none of the references, alone or in combination with one another, nor with the Meeh reference, disclose the use of "a non-radioactive diagnostically effective compound" as recited in claim 38.

In view of the foregoing, Applicants respectfully submit the Examiner's rejection cannot be sustained and should be withdrawn. Applicants believe that claims, as amended, are in allowable form and earnestly solicit the allowance of claims 2–6 and 38–40.

Respectfully submitted,

Royal N. Ronning, Jr., 32,529
Attorney for Applicants

Amersham Biosciences Corp
800 Centennial Avenue
P. O. Box 1327
Piscataway, New Jersey 08855-1327

Tel: (732) 457-8423
Fax: (732) 457-8463

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 19 June 2002.

Melissa Lock
Signature
Date June 19, 2002

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Claims (marked-up version showing amendments)

4. (twice amended) A method as claimed in claim 38, wherein vascular collateralization of the embolized vasculature is absent or sufficiently delayed such that said [reduced perfusion]composition is therapeutically effective.

6. (three times amended) A method as claimed in claim [38]5, wherein said[said] insoluble phosphate salt is hyroxyapatite, $Ca_{10}(PO_{[1]4})_6OH_2$.

38. (once amended) A method of embolus therapy comprising introducing a composition into the vasculature of a human or non-human animal subject, wherein said composition includes water insoluble particles 1-50 micrometers in size consisting essentially of a non-radioactive diagnostically effective compound or solution thereof encapsulated in a non-polymeric particulate matrix.

39. (once amended) [A]The method of claim 38 wherein the non-polymeric particulate matrix is selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, and ceramic particles.

Claims (clean version encompassing amendments)

2. (once amended) A method as claimed in claim 38, wherein said particles are 5-25 micrometers in size.

3. (once amended) A method as claimed in claim 38, wherein said particles are 10-20 micrometers in size.

C1

4. (twice amended) A method as claimed in claim 38, wherein vascular collateralization of the embolized vasculature is absent or sufficiently delayed such that said composition is therapeutically effective.

5. (twice amended) A method as claimed in claim 38, wherein said water-insoluble particles comprise an insoluble phosphate salt of the formula

$$M_{10}(PO_4)_6A_z$$

wherein

M = Ba, Ca, Cd, Mg, Pb or Sr

A = OH^-, Cl^-, F^- or CO_2^{-2}

Z = 2 if A is univalent, 1 if A is divalent.

C2

6. (three times amended) A method as claimed in claim 5, wherein said insoluble phosphate salt is hyroxyapatite, $Ca_{10}(PO_4)_6OH_2$.

C3

38. (once amended) A method of embolus therapy comprising introducing a composition into the vasculature of a human or non-human animal subject, wherein said composition includes water insoluble particles 1-50 micrometers in size consisting essentially of a non-radioactive diagnostically effective compound or solution thereof encapsulated in a non-polymeric particulate matrix.

39. (once amended) The method of claim 38 wherein the non-polymeric particulate matrix is selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, and ceramic particles.

40. The method of claim 38 wherein the diagnostically effective compound is an iodinated contrast agent, MR active agent, or ultrasound contrast agent imageable marker.